JAPANESE PATENT OFFICE
PATENT JOURNAL (A)
KOKAI PATENT APPLICATION NO. HEI 2[1990]-212488

Int. Cl.^{5}:	C 07 D 487/04 A 61 K 31/505 //A 61 K 7/06
Sequence Nos. for Office Use:	8413-4C 7375-4C
Filing No.:	Hei 1[1989]-32929
Filing Date:	February 13, 1989
Publication Date:	August 23, 1990
No. of Claims:	1 (Total of 11 pages)
Examination Request:	Not filed

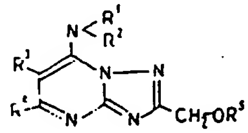
TRIAZOLOPYRIMIDINE DERIVATIVE

Inventor:	Shinichiro Shimizu 3-25 Hanasono-cho, Mukawa-cho, Yufutsu-gun, Hokkaido
Applicant:	Shinichiro Shimizu 3-25 Hanasono-cho, Mukawa-cho, Yufutsu-gun, Hokkaido

[Attached amendments have been incorporated into text of translation.]

Claim

A type of compound represented by the following formula:



(I)

[where R^1 and R^2 independently represent a hydrogen atom, lower alkyl group, or aralkyl group; R^3 represents a hydrogen atom or lower alkyl group; R^4 represents a hydrogen atom, lower alkyl group, or trifluoromethyl group; also, R^3 and R^4 may be combined to represent a bivalent alkylene group; R^5 represents a hydrogen atom, nitro group, carboxylic ester residual group; -$CONR^6R^7$ (R^6 and R^7 independently represent a hydrogen atom or lower alkyl group)].

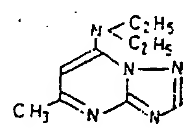
Detailed explanation of the invention

Industrial application field

This invention provides a novel type of triazolopyrimidine derivative. This novel type of compound can be used in preventing and treating diseases of the circulatory system, in particular, cerebral ischemia. In addition, it can also be used as a drug in treating migration of cancer cells, stomach ulcers, skin diseases, etc., and in promoting hair growth.

Prior art and problems to be solved

The following compound



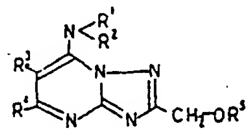
is commercially available under the generic name trapidil. This compound has a coronary circulation effect and thromboxane A_2 synthesis inhibiting effect, and it is used in treating stenocardia. However, the effects are insufficient. Also, this compound has a narrow range of application, as it is effective only in treating stenocardia.

In recent years, as life expectancy has improved significantly around the world, senile dementia has becomes a major social problem.

Types of senile dementia include Alzheimer's, the cause of which has not yet been determined, and the type due to cerebral arteriosclerosis. With this type, arteriosclerosis occurs in the walls of cerebral blood vessels, so that the supply of oxygen, enzymes, nutrients, etc. needed for metabolism by cerebral cells degrades, leading to inhibition of cerebral metabolism. This leads to blood vessel type dementia. According to the survey may by the Ministry of Health and Welfare in 1987 on senile medicines across Japan, about 60% of long-term hospitalized patients 65 or older have experience cerebral hemorrhage, high blood pressure, and heart disease. If patients with senile dementia are added to said proportion of 60%, one can see that almost all senile diseases are those pertaining to the circulatory system. In consideration of this background, the present inventors performed extensive studies on the development of a drug with a higher activity. As a result of such studies, a novel type of triazolopyrimidine derivative was synthesized. As a result, this invention was reached.

Constitution of the invention

This invention provides a type of compound represented by the following formula:



(I)

[where R^1 and R^2 independently represent a hydrogen atom, lower alkyl group, or aralkyl group; R^3 represents a hydrogen atom or lower alkyl group; R^4 represents a hydrogen atom, lower alkyl group, or trifluoromethyl group; also, R^3 and R^4 may be combined to represent a bivalent alkylene group; R^5 represents a hydrogen atom, nitro group, carboxylic ester residual group, -CONR^{6}R^7 (R^6 and R^7 independently represent a hydrogen atom or lower alkyl group)].

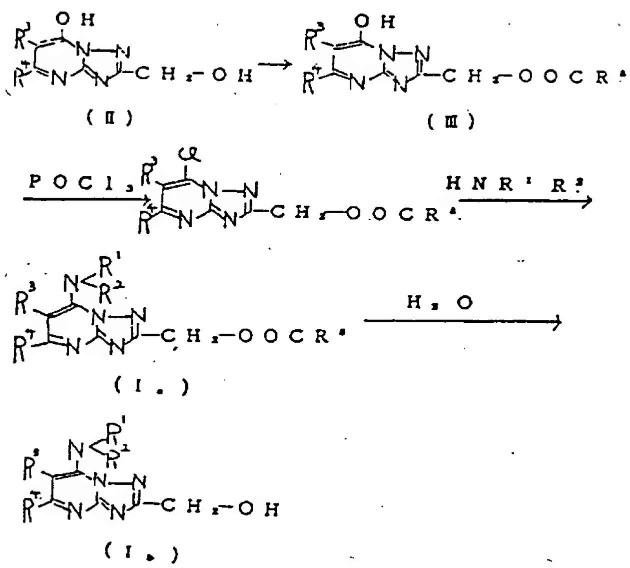
In said formula (I), preferable examples of the lower alkyl groups and aralkyl groups as R^1 and R^2 include methyl, ethyl, n-propyl, isopropyl, n-butyl, benzyl, 2-chlorobenzyl, 4-chlorobenzyl, etc.

R^3 represents a hydrogen atom or lower alkyl group, such as C1-4 groups. Examples include methyl, ethyl, n-propyl, isopropyl, butyl, etc. R^4 represents a hydrogen, lower alkyl group, or trifluoromethyl group. The lower alkyl groups refer to C1-4 groups in this case. Examples include methyl, ethyl, n-propyl, isopropyl, butyl, etc. Also, R^3 and R^4 may combine to form a bivalent alkylene group. R^5 represents a hydrogen atom, nitro group, carboxylic ester residual group, or -CONR^{6}R^7 (R^6 and R^7 independently represent a hydrogen atom or C1-5 alkyl group). Any carboxylic acid may be used as the fatty acid for esterification of these groups. Examples include acetic acid, propionic acid, butyric acid, cyclohexanecarboxylic acid, cyclopentanecarboxylic acid, capric acid, caproic acid, undecanoic acid, lauric acid, palmitic acid, myristic acid, stearic acid, pentadecanoic acid, 10-undecylenic acid, palmitoleic acid, palmitoelaidic acid, elaidic acid, linolic acid, α-linoleic acid, 5,8,11,14,17-eicosapentenoic acid, 4,7,10,13,16,19-docosahexenoic acid, 6,9,12,15-octadecatetraenoic acid, thioctic acid, retinoic acid, farnesylacetic acid, benzoic acid, 4-methoxybenzoic acid, 2-methoxybenzoic acid, 3,4-dimethoxybenzoic acid, 3,4,5-trimethoxybenzoic acid, 2,3,4-trimethoxybenzoic acid, 2-nitrobenzoic acid, 3-nitrobenzoic acid, 4-nitrobenzoic acid, phenylacetic acid, 4-chlorophenylacetic acid, 2-(4-chlorophenoxy)-2-methylpropionic acid, salicylic acid, acetylsalicylic acid, cinnamic acid, 4-methoxycinnamic acid, 3,4-dimethoxycinnamic acid, 3,4,5-trimethoxycinnamic acid, 2,3,4-trimethoxycinnamic acid, nicotinic acid, carbamic acid, N-methylcarbamic acid, N-dimethylcarbamic acid, etc.

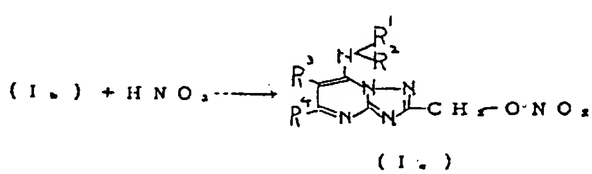
Detailed explanation of the invention

The novel triazolopyrimidine derivative represented by said formula (I) in this invention can be manufactured using various methods. In the following, several major reaction examples will be explained.

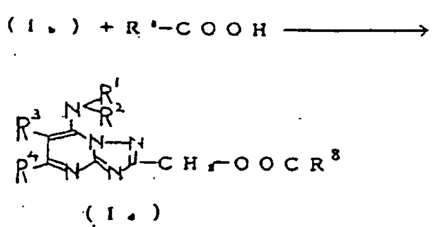
Method A



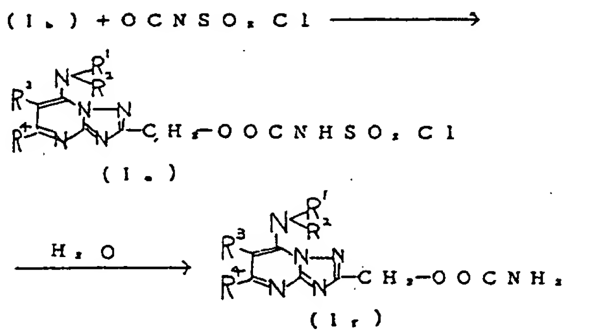
Method B



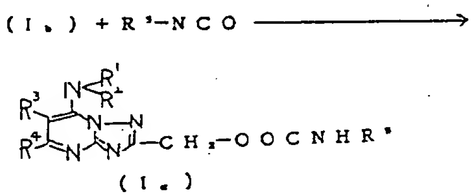
Method C



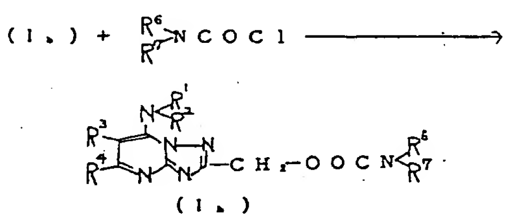
Method D



Method E



Method F



(where R^a-COOH represents the carboxylic acid mentioned in the claims of this invention or a carboxylic acid as a protecting group; R[illegible] represents a C1-5 lower alkyl group; other symbols are the same as aforementioned).

Starting substance (II) in method (A) is usually a well known compound (US Patent No. 2835581, Eastman Kodak Co.) or a compound that can be obtained using a similar method.

The esterification of compound (II) and R^a-COOH can be performed as a conventional organic chemical reaction, that is, a reaction using an acid halide, acid anhydride, or mixed acid anhydride. It may also be performed as a reaction in the presence of carbonyldiimidazole, dicyclohexylcarbodiimide, or Meyer's reagent in an inactive organic solvent, such as dimethylpyrrolidone, dimethyl sulfoxide, acetonitrile, or other solution. In this reaction, compound (III) can be obtained easily.

The reaction between compound (III) and phosphorus oxychloride may be performed without a catalyst or in the presence of dimethylaniline, pyridine, or triethylamine. Usually, excess phosphorus oxychloride is used and the reaction is performed without a catalyst. The

reaction is performed at 40-100°C for 30 min to 2 h. After the reaction, the excess phosphorus oxychloride is recovered under a reduced pressure.

The residue containing compound (IV) is refined using a conventional method. Compound (IV) and amine are usually reacted by adding amine to methanol or an ethanol solution of compound (IV) cooled with ice. The reaction is carried out at room temperature and terminates in 0.5-2 h. After the reaction, alcohol is distilled off under reduced pressure, and the residue is refined using a conventional method. As a result, target compound (I_b) of this invention is obtained. In addition, treatment is performed by means of an aqueous solution of sodium hydroxide or potassium hydroxide to obtain compound (I_b). This compound is also a target compound of this invention. Also, it may be used as a starting compound.

In method (B), the reaction between compound (I_b) and nitric acid is carried out as a conventional nitration reaction. For example, the reaction between compound (I_b) and a mixed liquid of fuming sulfuric acid and concentrated nitric acid, a mixed liquid of concentrated nitric acid and acetic anhydride, or a mixed liquid of potassium nitrate and concentrated sulfuric acid under cooling to -10 to 20°C for 0.5-2 h. After the reaction, treatment is carried out using a conventional method. The obtained compound is refined by means of column chromatography, recrystallization, or the like. In method (C), the reaction between compound (I_b) and a carboxylic acid is usually performed with carboxylic acid as a reactive derivative. For example, an acid halide, acid anhydride, or a mixed acid anhydride can be used preferably in this case. The reaction is usually carried out in an inactive organic solvent and in the presence of a deoxidant. Examples of inactive organic solvents include methylene chloride, chloroform, dimethylformamide, tetrahydrofuran, acetone, acetonitrile, etc.

The temperature is in the range of -10~50°C. The end point of the reaction is checked by means of thin-layer chromatography that determines the absence of starting material.

Examples of deoxidants that can be used in this invention include tertiary amines, such as pyridine, picoline, triethylamine, trimethylamine, etc. After the reaction, separation and refinement are carried out using a conventional method. For example, one may adopt silica column chromatography, recrystallization, etc. When direct reaction is performed between compound (I_b) and a carboxylic acid, one should make use of a condensing agent. In the presence of a condensing agent, such as carbonyldiimidazole, dicyclohexylcarbodimide, Meyer's reagent, or the like, reaction is performed in an inactive organic solvent. Examples of inactive organic solvents include methylene chloride, chloroform, tetrahydrofuran, acetone, dioxane, acetonitrile, ethyl acetate, dimethylformamide, etc.

The temperature is in the range of 10-50°C. Progress of the reaction is checked by means of thin-layer chromatography. After the end of the reaction, separation and refinement are carried out using a conventional method.

In method (D), the reaction between compound (I_b) and chlorosulfonyl isocyanate is carried out as a solution of compound (I_b) in an inactive organic solvent cooled with ice, while a solution of chlorosulfonyl isocyanate in an inactive organic solvent is added a little at a time, followed by reaction at room temperature for 0.5-2 h to form compound ($I_{[illegible]}$). Then, without separation, decomposition is performed by means of an aqueous solution of hydrochloric acid to form compound (I_t).

In method $(E)_f$, the reaction between compound (I_b) and a lower alkyl isocyanate is performed in an inactive organic solvent. Examples of the inactive solvents that may be used include methylene chloride, chloroform, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, acetonitrile, etc. The reaction is performed at 0°C-80°C. Preferable catalysts include tertiary amines, such as triethylamine, dimethylaminopyridine, DBU, DBN, triethylenediamine, as well as organic tin compounds. After the reaction, the reaction mixture is heated under reduced pressure to distill off the used organic solvent. The residue is refined using a conventional method to form compound (I_g).

In method (F), the reaction between compound (I_b) and a di-lower alkyl carbamoyl chloride is performed in an inactive organic solvent. Examples of the inactive organic solvents that may be used include methylene chloride, chloroform, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, acetonitrile, etc. In this case, a tertiary amine is used as a deoxidant. Examples of the tertiary amines that may be used include triethylamine, pyridine, picoline, etc. The reaction temperature is in the range of -50°C to 50°C. After the end of the reaction, the reaction mixture is heated under reduced pressure to remove the organic solvent. The residue is refined using a conventional method to form compound (I_h).

The triazolopyrimidine derivative represented by formula (I) in this invention has a coronary artery expansion effect and the effect of inhibiting biosynthesis of prostaglandins and thromboxane A_2, and it can be used in treating and preventing various diseases of the circulatory system, in particular, diseases of cerebral circulatory organs, of mammals, such as cerebral arteriosclerosis, cerebral thrombosis, cerebral infarction, cerebral metabolism sthenia, senile dementia, sequellae of cerebral hemorrhage and other cerebral diseases, as well as stenocardia, cardiac infarction, arteriosclerosis, hyperlipidemia, etc. Also, it can be used as a drug in treating the migration of cancer cells, stomach ulcers, skin diseases, etc., and in promoting hair growth.

Any administration method appropriate for the specific case can be adopted for administering the compound of this invention. It can be processed to form various formulations, including nonoral and oral injection formulations. When formulations are prepared, one may make use of various excipients, such as starch, cellulose derivatives, gum arabic, stearic acid, calcium phosphate, talc, alginic acid, mannitol, ethanol, glycerin, etc. The compound may be processed to any form desired for the administration method. Forms of formulations include

tablets, powders, capsules, granules, triturated powders, lozenges, emulsions, suspensions, and cataplasms. Also, compound (I) may be formed as clathrates of cyclodextrin or methylcyclodextrin, and it may be enclosed in liposomes. Also, it may be prepared as an ointment, cream, lotion, spray, etc. for application to the skin.

The daily dose of the compound of this invention for each object depends on whether the object is a person or an animal, and, if an animal, the species of the animal, as well as the body weight and the type of the disease. Typically, the daily dose for an adult should be in the range of 50-3000 mg. It may be administered in 1-3 rounds.

In the following, this invention will be explained in detail with reference to application examples. However, this invention is not limited to these application examples.

Reference Example 1

160 g of 2-hydroxy-5-methyl-s-triazolo[1,5-a]pyrimidin-7-ol were dissolved in 1.1 L of dimethylformamide. Then, 640 mL of acetic anhydride and 10 g of p-toluenesulfonic acid were added, and the mixture was heated at 70°C and agitated for 22 h. At the same temperature, the mixture was concentrated under a reduced pressure. Ethyl ether was added to the deposited residue, and the mixture was filtered, followed by washing with ethyl ether and drying. Then, methanol was used for recrystallization, forming 120 g of 2-acetoxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidin-7-ol.

Reference Example 2

While 300 mL of phosphorus oxychloride were cooled with ice, 68 mL of dimethylaniline were added dropwise. After 60 g of 2-acetoxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidin-7-ol were added, the mixture was agitated at 50-60°C for 1 h. Then, the excess phosphorus oxychloride was distilled off.

800 mL of chloroform were added to the residue to dissolve it. After a few rounds of washing with ice water, the residue was dried by means of anhydrous magnesium sulfate, and the solvent was distilled off. Then, isopropyl ether was added to the residue, and the mixture was filtered and dried, forming 63 g of 2-acetoxymethyl-5-methyl-7-chloro-s-triazolo[1,5-a]pyrimidine.

^{1}H-NMR ($CDCl_3$ + d_6-DMSO) δ
2.23 (s, 3H), 2.80 (s, 3H)
5.48 (s, 2H), 7.53 (s, 1H)

Application Example 1

24 g of 2-acetoxymethyl-5-methyl-7-chloro-s-trizolo[1,5-a]pyrimidine were suspended in 300 mL of ethanol. Under cooling with ice, 31 mL of diethylamine were added dropwise in 15 min, followed by agitation at room temperature for 1 h. Then, methanol was distilled off, and ethyl ether was added to the residue. The deposited diethylamine hydrochloride was filtered off, and ethyl ether was distilled off, forming 25 g of 7-diethylamino-2-acetoxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine.

^{1}H-NMR ($CDCl_3$) δ:
1.35 (t, J=7Hz, 6H)
2.18 (s, 3H), 2.53 (s, 3H)
3.88 (q, J=7Hz, 4H)
5.37 (s, 2H), 6.14 (s, 1H)

Application Example 2

300 mL of a 10% aqueous solution of potassium hydroxide were added to 25 g of 7-diethylamino-2-acetoxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine, followed by agitation at room temperature for 1 h. The obtained solution was fed to flow in a 100-mL column of Diaion HP-20 (product of Mitsubishi Chemical Co., Ltd.), and was washed with water until it became neutral. Then, methanol was used for elution. The fractions containing the target compound were combined, followed by distillation to remove the solvent, forming 18.5 g of 7-diethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine.

Melting point: 157-160°C

^{1}H-NMR ($CDCl_3$) δ:
1.34 (t, J=7Hz, 6H)
2.57 (s, 3H)
3.94 (q, J=7Hz, 4H)
5.03 (s, 2H), 6.12 (s, 1H)

Application Example 3

36 g of 2-acetoxymethyl-5-methyl-7-chloro-s-triazolo[1,5-a]pyrimidine were suspended in 400 mL of methanol. Then, under cooling with ice, 50 mL of a 40% aqueous solution of dimethylamine were added dropwise over 15 min, followed by agitation at room temperature for 1 h. Then, the solvent was removed by distillation. Then, 400 mL of a 10% aqueous solution of potassium hydroxide were added, and the mixture was agitated at room temperature. As a result, a large amount of crystals were deposited. After 1 h, the crystals were filtered out and washed with water and dried, forming 25.5 g of 7-dimethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine.

Melting point: 217-220°C

^1H-NMR (d_6-DMSO) δ:
2.48 (s, 3H), 3.44 (s, 6H)
4.68 (s, 2H), 6.38 (s, 1H)

Application Example 4

7.2 mL of concentrated sulfuric acid (d=1.84) were cooled with an ice-salt mixture. Then, 5.4 mL of fuming sulfuric acid were added dropwise. 3.53 g of 7-diethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine were added to the mixed solution. The mixture was agitated while being cooled for 30 min and then at room temperature for 1 h 30 min. The mixture was poured into 60 mL of ice water and then agitated while being cooled. Then, sodium carbonate powder was added for neutralization to pH 8. 150 mL of tetrahydrofuran were used for extraction, followed by drying with anhydrous magnesium sulfate and removal of the solvent by means of distillation. The obtained yellow oil-like substance was analyzed by silica chromatography, forming 4.52 g of 7-diethylamino-2-nitratomethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as yellow crystals.

Melting point: 108-110°C

IR 840 cm^{-1} 1640 cm^{-1} ($-ONO_2$)
^1H-NMR ($CDCl_3$) δ:
1.37 (t, J = 7Hz, 6H)
2.54 (s, 3H)
3.93 (q, J = 7Hz, 4H)
5.86 (s, 2H), 6.17 (s, 1H)

Application Example 5

The operation was performed in the same way as in Application Example 4, forming 7-dimethylamino-2-nitratomethyl-5-methyl-s-triazolo[1,5-a]pyrimidine.

Melting point: 134-135°C

IR 840 cm^{-1} 1280 cm^{-1}
1640 cm^{-1} ($-ONO_2$)
^1H-NMR ($CDCl_3$) δ:
2.57 (s, 3H), 3.50 (s, 6H)
5.80 (s, 2H), 6.12 (s, 1H)

Application Example 6

30 mL of thionyl chloride were added to 7.27 g of pentadecanoic acid, followed by heating with reflux for 3 h. Then, the excess thionyl chloride was distilled off, and the residue was dissolved in 50 mL of methylene chloride. The solution was added dropwise under ice cooling to a solution of 3.106 g of 7-dimethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine and 100 mL of methylene chloride and 418 mL of triethylamine. After being allowed to stand at room temperature for 1 h, the solvent was distilled off. 100 mL of

chloroform were added to the residue, and the mixture was washed with a 5% solution of sodium hydrogen carbonate, followed by drying with anhydrous magnesium sulfate. Then, silica gel chromatography was performed for purification , forming 9.2 g of 7-dimethylamino-2-pentadecanoyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as colorless crystals.

Melting point: 92-93°C

^{1}H-NMR ($CDCl_3$) δ:
0.77~2.68 (m, 32H)
3.48 (s, 6H), 5.42 (s, 2H)
6.06 (s, 1H)

Application Example 7

The operation was performed in the same way as in Application Example 6, forming 7-dimethylamino-2-pentadecanoyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine.

Melting point: 69-71°C

^{1}H-NMR ($CDCl_3$) δ:
0.70~2.61 (m, 38H)
3.90 (q, J=7Hz, 4H)
5.38 (s, 2H), 6.04 (s, 1H)

Application Example 8

The operation was performed in the same way as in Application Example 6, forming 7-dimethylamino-2-linolylmethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as an oil-like substance.

^{1}H-NMR ($CDCl_3$) δ:
0.74~3.10 (m, 36H)
3.91 (q, J=7Hz, 4H)
5.36~5.70 (m, 6H)
6.08 (s, 1H)

Application Example 9

The operation was performed in the same way as in Application Example 6, forming 7-dimethylamino-2-linolylmethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as a paste-like substance.

^{1}H-NMR ($CDCl_3$) δ:
0.74~3.10 (m, 30H)
3.48 (s, 6H)
5.37~5.70 (m, 6H)
6.08 (s, 1H)

Application Example 10

The operation was performed in the same way as in Application Example 6, forming 7-dimethylamino-2-linoleyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as an oil-like substance.

¹H-NMR ($CDCl_3$) δ:
0.83~2.98 (m, 32H)
3.90 (q, J=7Hz, 4H)
5.35~5.60 (m, 8H)
6.07 (s, 1H)

Application Example 11

The operation was performed in the same way as in Application Example 6, forming 7-dimethylamino-2-linoleyloxymethyl-s-triazolo[1,5-a]pyrimidine as a paste-like substance.

¹H-NMR ($CDCl_3$) δ:
0.86~3.15 (m, 26H)
3.50 (s, 6H)
5.37~563 (m, 8H)
6.08 (s, 1H)

Application Example 12

A mixed solution of 1.65 g of 7-dimethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine in 50 mL of methylene chloride and 2.09 mL of triethylamine was cooled with ice. A solution of 4.5 g of oleic acid chloride in 20 mL of methylene chloride was added dropwise to said solution. After 30 min, the reaction solution was washed with a 5% aqueous solution of sodium hydrogen carbonate, and dried with anhydrous magnesium sulfate, followed by removal of the solvent with distillation and then refinement with silica gel chromatography, forming 4.2 g of 7-dimethylamino-2-oleyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as an oil-like substance.

¹H-NMR
0.75~2.70 (m, 37)
2.57 (s, 3H)
3.94 (q, J=7Hz, 4H)
5.35~5.68 (m, 2H)
5.42 (s, 2H)
6.08 (s, 1H)

Application Example 13

The operation was performed in the same way as in Application Example 12 to form 7-dimethylamino-2-oleyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as a paste-like substance.

¹H-NMR
0.75~2.62 (m, 31H)
2.52 (s, 3H)
3.43 (s, 6H)
5.30~5.54 (m, 4H)
6.02 (s, 1H)

Application Example 14

The operation was performed in the same way as in Application Example 12 to form 7-dimethylamino-2-undecylenyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as an oil-like substance.

^{1}H-NMR
1.25~2.78 (m, 16H)
2.60 (s, 3H), 3.53 (s, 6H)
4.93~6.22 (m, 3H)
5.48 (s, 2H), 6.12 (s, 1H)

Application Example 15

The operation was performed in the same way as in Application Example 12 to form 7-diethylamino-2-undecylenyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as an oil-like substance.

^{1}H-NMR
1.24~2.67 (m, 22H)
2.57 (s, 3H)
3.95 (q, J=7Hz, 4H)
4.90~6.08 (m, 3H)
5.42 (s, 2H), 6.10 (s, 1H)

Application Example 16

4.5 g of cis-5,8,11,14,17-eicosapentaenoic acid were dissolved in 80 mL of methylene chloride. Then, a solution of 8 mL of oxalyl chloride and 10 mL of methylene chloride was added dropwise in 10 min. Then, the mixture was agitated at room temperature for 30 min. The reaction solution was then concentrated. 10 mL of methylene chloride were added to the obtained oil-like residue to form a solution. The solution was added dropwise during 10 min to a solution of 2.35 g of 7-diethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine, 70 mL of methylene chloride, and 2.8 mL of triethylamine under ice cooling while being agitated followed by stirring at room temperature for 30 min. After the reaction solution was washed with a 5% aqueous solution of sodium hydrogen carbonate, it was dried with anhydrous magnesium sulfate. The solvent was distilled off, and the obtained oil-like substance was refined with silica gel chromatography, forming 3.15 g of 7-diethylamino-2-(cis-5,8,11,14,17-eicosapentaenoyl)oxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as an oil-like substance.

^{1}H-NMR ($CDCl_3$) δ:
0.98 (t, J=7Hz, 3H)
1.34 (t, J=7Hz, 3H)
1.68~3.14 (m, 16H)
2.54 (s, 3H)
3.88 (q, J=7Hz, 4H)
5.33~5.77 (m, 12H)
6.04 (s, 1H)

Application Example 17

The operation was performed in the same way as in Application Example 16, forming 7-dimethylamino-2-(cis-5,8,11,14,17-eicosapentaenoyl)oxymethyl-5-methyl-s-triazolo[1,5-a] pyrimidine as an oil-like substance.

^{1}H-NMR ($CDCl_3$) δ:
0.97 (t, J=7Hz, 3H)
1.26~3.24 (m, 16H)
2.53 (s, 3H)
3.45 (s, 6H)
5.33~5.67 (m, 12H)
6.02 (s, 1H)

Application Example 18

The operation was performed in the same way as in Application Example 16, forming 7-diethylamino-2-retinoyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as an oil-like substance.

^{1}H-NMR δ:
1.05 (s, 6H)
1.35 (t, 6H)
1.44~2.28 (m, 15H)
2.56 (s, 3H)
3.88 (q, 4H)
5.18~7.12 (m, 6H)
5.40 (s, 2H)
6.03 (s, 1H)

Application Example 19

2.07 g of 7-dimethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine were suspended in 25 mL of pyridine and 20 mL of dimethylformamide. 2.14 g of nicotinic acid hydrochloride were added to the solution at room temperature. The solution was almost transparent. However, after a while, it became turbid entirely. After being allowed to stand for 30 min, the liquid was heated and agitated in an oil bath at 110°C, forming a transparent liquid. It was then cooled, and crystal were deposited. The crystals were filtered out and washed with methanol, followed by drying. By means of methanol, they were recrystallized, forming 2.26 g of 7-dimethylamino-2-nicotinoyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as light yellowish crystals.

Melting point: 183°C

^{1}H-NMR (d_6-DMSO) δ:
2.47 (s, 3H)
3.45 (s, 6H)
5.66 (s, 2H)
6.46 (s, 1H)
7.53~9.48 (m, 4H)

Application Example 20

2.35 g of 7-diethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine were dissolved in 20 mL of pyridine and 10 mL of dimethylformamide. 2.14 g of nicotinic acid hydrochloride were added to the solution at room temperature. The liquid was heated and agitated in an oil bath at 85°C, followed by drying under reduced pressure at the same temperature. Chloroform was added to dissolve it, and water washing was performed, followed by drying with magnesium sulfate. It was then heated under reduced pressure to remove chloroform by distillation. The residue was refined by silica gel chromatography, forming 2.63 g of 7-diethylamino-2-nicotinoyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as a white powder.

Melting point: 126°C

^{1}H-NMR (d_6-DMSO) δ:
1.23 (t, J=7Hz, 6H)
2.52 (s, 3H)
3.87 (q, J=7Hz, 4H)
5.70 (s, 2H)
6.45 (s, 1H)
7.63~9.46 (m, 4H)

Application Example 21

1.18 g of 7-diethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine, 1.45 g of thioctic acid, and 40 mg of dimethylaminopyridine were dissolved in 20 mL of methylene chloride. 1.45 g of dicyclohexylcarbodiimide were added to the solution, and the mixture was agitated for 4 h at room temperature. The deposited crystals were filtered off, and the filtrate was washed with water, a 5% solution of sodium hydrogen carbonate and then water again, followed by drying with magnesium sulfate. Then, methylene chloride was distilled off under a reduced pressure. The residue was refined by silica gel chromatography, forming 1.75 g of 7-diethylamino-2-thioctyloxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine as a light-yellowish oil-like substance.

^1H-NMR (d_6-DMSO) δ:
1.33 (t, J=7Hz, 6H)
1.28~3.34 (m, 13H)
2.51 (s, 3H)
3.88 (q, J=7Hz, 4H)
5.38 (s, 2H)
6.07 (s, 1H)

Application Example 22

1.044 mL of chlorosulfonyl isocyanate were dissolved in 30 mL of methylene chloride, and the solution was cooled with ice. A solution of 2.35 g of 7-diethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine in 30 mL of methylene chloride was added to said solution in 30 min while being cooled with ice. After agitation under ice cooling for 30 min and then at room temperature for 1.5 h, 10 mL of 2N hydrochloric acid were added, and the mixture was agitated for 1 h. Then, the mixture was heated under reduced pressure, and the volatile component was distilled off. As a result, a transparent millet jelly-like substance was obtained. It was dissolved in ethanol, followed by distillation under reduced pressure. After this operation was performed repeatedly for several rounds, moisture was entirely removed to form a foam-like substance. As a result, 3.4 g of 7-diethylamino-5-methyl-s-triazolo[1,5-a]pyrimidine-2-methanol carbamate were obtained in the form of a white powder.

^1H-NMR (d_6-DMSO) δ:
1.32 (t, J=7Hz, 6H)
2.56 (s, 3H)
4.09 (q, J=7Hz, 4H)
5.24 (s, 2H)
6.84 (s, 1H)

Application Example 23

1.035 g of 7-dimethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine were dissolved in 40 mL of dimethylformamide. 1.1 mL of methyl isocyanate and 1 appropriate [sic, 1 drop] of tributyltin oxide solution were added, followed by heating at 40°C for 6 h and then drying under a reduced pressure. The residue was washed with isopropyl ether and recrystallized with acetonitrile, forming 1 g of 7-dimethylamino-5-methyl-s-triazolo[1,5-a]pyrimidine-2-methanol-N-methyl carbamate as light-yellowish crystals.

Melting point: 186-187°C

^1H-NMR (d_6-DMSO) δ:
2.48 (s, 3H)
2.70 (d, J=5Hz, 3H)
3.47 (s, 6H)
5.27 (s, 2H)
6.41 (s, 1H)
7.34 (m, 1H)

Application Example 24

1.18 g of 7-diethylamino-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine were dissolved in 20 mL of dimethylformamide. 1 mL of methyl isocyanate and 1 appropriate [sic, 1 drop] of tributyltin oxide solution were added, followed by agitation at room temperature overnight. It was then heated under reduced pressure and evaporated and dried. The residue was washed with isopropyl ether and recrystallized with an acetonitrile-ethyl acetate mixed solution, forming 1.31 g of 7-diethylamino-5-methyl-s-triazolo[1,5-a]pyrimidine-2-methanol-N-methyl carbamate as white crystals.

Melting point: 153°C

^1H-NMR (d_6-DMSO) δ:
1.28 (t, J=7Hz, 6H)
2.49 (s, 3H)
2.68 (d, J=5Hz, 3H)
3.88 (q, J=7Hz, 4H)
5.24 (s, 2H)
6.40 (s, 1H)
7.33 (m, 1H)

Application Example 25

(1) 4.81 g of 2-acetoxymethyl-5-methyl-7-chloro-s-triazolo[1,5-a]pyrimidine were suspended in 50 mL of methanol. Then, a solution of 4.8 mL of 2-chlorobenzylamine and 10 mL of methanol was added dropwise in 10 min to the suspension. After agitation at room temperature for 1 h, it was dried under reduced pressure, forming crude 7-(2-chlorobenzylamino)-2-acetoxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine.

(2) 50 mL of a 10% potassium hydroxide and 30 mL of methanol were added to said compound, and the mixture was agitated at room temperature. As a result, a large amount of crystal were deposited. After 1 h, the crystals were filtered out, washed with water and dried, forming 5.67 g of 7-(2-chlorobenzylamino)-2-hydroxymethyl-5-methyl-s-triazolo[1,5-a]pyrimidine.

Melting point: 211-212°C

^1H-NMR (d_6-DMSO) δ:
2.44 (s, 3H)
4.78 (s, 4H)
6.31 (s, 1H)
7.36~7.80 (m, 4H)

Reference Example 3

(1) 45 mL of ethyl-2-oxocyclopentane carboxylate and 43 g of 3-amino-5-hydroxymethyl-1,2,4-triazole glycolate were agitated in 100 mL of acetone at 110°C in an oil

bath for 4.5 h. While the mixture was warm, 100 mL of acetone were added, followed by cooling. The deposited crystals were filtered and washed with acetone, followed by drying, forming 34.18 g of 8-hydroxy-2-hydroxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine.

(2) 36 mL of acetic anhydride, 30 mL of pyrimidine, and 100 mL of methylene chloride were added to said compound, followed by heating with reflux for 4 h. Then, the mixture was cooled, and 30 mL of ethyl ether were added. The deposited crystals were filtered and washed with ethyl ether, followed by drying to form 29.19 g of 8-hydroxy-2-acetoxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine.

(3) 150 mL of phosphorus oxychloride were added to 29 g of said compound, followed by heating with reflux for 5 min. Then, the mixture was cooled with water, and the excess phosphorus oxychloride was distilled off under reduced pressure. 400 mL of methylene chloride and 300 mL of water were added to the residue, and the mixture was agitated. Then, the methylene chloride layer was collected, followed twice by water washing with 300 mL of water, followed by drying with anhydrous magnesium sulfate. Then, methylene chloride was distilled off. It was allowed to stand for crystallization. After washing with isopropyl ether, it was dried, forming 32.72 g of 8-chloro-2-acetoxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine.

Application Example 26

(1) 16.3 g of 8-chloro-2-acetoxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine were dissolved in 180 mL of methanol. While being agitated under ice cooling, 18.6 mL of diethylamine were added dropwise in 20 min, followed by agitation at room temperature for 2 h.

Then, methanol was distilled off, forming 8-diethylamino-2-acetoxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine as an oil-like substance.

(2) 180 mL of a 10% potassium hydroxide solution were added to said compound, and the entire solution was crystallized. 100 mL of water were added, and the mixture was agitated for 1 h. Then, the crystals were filtered, followed by water washing and drying. They were recrystallized with isopropanol, forming 10.21 g of 8-diethylamino-2-hydroxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine.

Melting point: 210-212°C (decomposition)

^1H-NMR (d_6-DMSO) δ:

1.15 (t, J = 7 Hz, 6H)

1.95~2.44 (m, 2H)

2.83~3.28 (m, 4H)

3.82 (q, J = 7 Hz, 6H)

4.68 (s, 2H)

Application Example 27

(1) 16.3 g of 8-chloro-2-acetoxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine were dissolved in 180 mL of methanol. 20 mL of a 40% aqueous solution of dimethylamine were added dropwise in 15 min to the solution under ice cooling. After agitation at room temperature for 1 h, it was dried under a reduced pressure, forming 8-dimethylamino-2-acetoxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine.

(2) 150 mL of a 10% aqueous solution of potassium hydroxide were added to said compound, and the mixture was agitated at room temperature for 1 h. The deposited crystals were filtered, washed with water and dried. The crystals were recrystallized with ethanol, forming 10.8 g of 8-dimethylamino-2-hydroxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo-[1,5-a]-pyrimidine

Melting point: 243-245°C (decomposition)

^1H-NMR (d_6-DMSO) δ:
1.97~2.38 (m, 2H)
2.78~3.32 (m, 4H)
3.42 (s, 6H)
4.70 (s, 2H)

Application Example 28

Under cooling with an ice-table salt mixture, 5.4 mL of fuming nitric acid were added dropwise to 7.2 mL of concentrated sulfuric acid (d=1.84). 3.92 g of 8-diethylamino-2-hydroxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine were added, a little at a time, in 15 min to said mixed solution. The mixture was agitated under ice cooling for 1 h, and then at room temperature for 1 h. The product was poured into 50 mL of ice water, and, while the mixture was agitated under ice cooling, sodium carbonate powder was added for neutralization to pH 8.

After extraction with a 30% tetrahydrofuan-ethyl acetate mixed solution, and washing with saturated saline, drying was performed with anhydrous magnesium sulfate, and the solvent was distilled off, forming 5.23 g of an oil-like substance. It was refined by silica gel column chromatography, forming 3.87 g of 8-diethylamino-2-nitratomethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine as an oil-like substance.

^1H-NMR ($CDCl_3$) δ:
1.25 (t, J=7Hz, 6H)
2.13~2.56 (m, 2H)
2.94~3.34 (m, 4H)
3.80 (q, J=7Hz, 4H)
5.83 (s, 2H)

Application Example 29

Using 8-dimethylamino-2-hydroxymethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine and in the same operation as in Application Example 28, one obtained 8-dimethylamino-2-nitratomethyl-6,7-dihydro-5H-cyclopenta-[d]-s-triazolo[1,5-a]pyrimidine.

Melting point: 82°C

^{1}H-NMR ($CDCl_3$) δ:
2.04~2.53 (m, 2H)
2.77~3.34 (m, 4H)
3.44 (s, 6H)
5.81 (s, 2H)